SASP. Because astrocytes have a critical role in the regulation of both synaptic function and cerebral blood flow and are directly exposed to tau at its site of release at the tripartite synapse, we conducted studies to define whether soluble aggregated tau propagates to astrocytes, inducing astrocyte senescence/SASP and neuronal dysfunction/damage. Our studies indicate that tau can be propagated transcellularly to astrocytes, triggering cellular senescence/SASP. Our studies suggest that astrocyte senescence is detrimental to dendritic and synaptic structure and density, suggesting that pathogenic soluble tau-induced astrocyte senescence may contribute to synaptic dysfunction and loss in AD. Drugs that eliminate senescent cells are FDA-approved and antibody-based approaches to remove tau from brain are already in clinical trials. Our studies suggest that these interventions could be effective in the treatment of AD and other tauopathies.

TYPE I INTERFERON-MEDIATED NEUROINFLAMMATORY PROGRAM AND SYNAPSE LOSS IN ALZHEIMER'S DISEASE

Ethan Roy,[1] Baiping Wang,[1] Hui Zheng,[1] and Wei Cao[1], *1. Baylor College of Medicine, Houston, Texas, United States*

The cytokine family type I interferon (IFN) is a major innate immune mediator extensively studied in the peripheral immune responses but largely under-investigated in AD. Previously, we established that innate immune cells readily produce IFN in response to amyloid fibrils containing nucleic acids as cofactor. Here, we investigated whether IFN pathway is associated with amyloidosis in AD brain and contributes to neuroinflammation. By systemically characterizing neuroinflammation in multiple murine AD models, we established a comprehensive core AD neuroinflammation profile that includes several key proinflammatory cytokine families, among which IFN pathway is consistently activated. When hippocampal slice culture was stimulated with different forms of amyloid fibrils, nucleic acid-containing amyloid fibrils, but not heparin-containing fibrils, potently activated IFN pathway and triggered comprehensive neuroinflammation. In addition, stereotaxic administration of IFNβ induced an immune response in the brain of wild type mice analogous to the core neuroinflammatory profile associated with Aβ pathology; whereas selective IFN receptor blockade significantly blunted the ongoing microgliosis in AD models in vivo. Furthermore, IFN promoted microglia-mediated synapse uptake from neurons, which depended on the induction of complement C3, and blockade of IFN signaling significantly abolished the pathogenic synapse loss in AD brain. Consistent with the findings in mice, we found that genes stimulated by IFN were grossly upregulated in human AD brains. Therefore, type I interferon constitutes a major pathway within the neuroinflammatory network of AD and may represent a molecular target to restrain the pathogenic inflammatory responses.

METABOLOMICS OF DELIRIUM: A CASE-CONTROL STUDY

Bridget Tripp,[1] Simon Dillon,[2] Sarinnapha Vasunilashorn,[2] Long H. Ngo,[2] Tamara G. Fong,[2] Edward R. Marcantonio,[2] Towia A. Libermann,[2] and Hasan Otu[1], *1. University of Nebraska-Lincoln, Lincoln, Nebraska, United States, 2. Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States*

Postoperative delirium complicates 15-50% of major surgery in older adults, resulting in poor patient outcomes and increased healthcare costs. Basic mechanisms of delirium are largely unknown. In this study we implemented a protocol that uses high-throughput metabolomics to explore potential biological mechanisms of delirium. We profiled the plasma metabolome of 10 delirium cases and 10 matched controls from the SAGES cohort of older adults without dementia undergoing major non-cardiac surgery. We used targeted mass spectrometry to measure 302 metabolites (features) preoperatively (PREOP) and on postoperative day 2 (POD2). Metabolomics studies are challenged by inherent technical variability and signal noise. With a small sample and a large feature count, signal noise diminishes statistical power and masks true biological signals. To address these challenges, we implemented quality control sample-based signal correction and normalization to internal standards (ISs). ISs were screened from a pool of 6 potential candidates, resulting in the removal of 3 that failed to perform well, while 3 were retained for our experiments. ISs also enabled successful concatenation of experiments run at different times. Prior to implementing quality control samples and customized ISs, no metabolites were identified as differentially expressed. After implementation, we identified one metabolite that was significantly differentially expressed at PREOP and 17 metabolites that were significantly differentially expressed at POD2 between delirium and controls (BH-corrected p-value < 0.05). In conclusion, integration of quality controls and normalization to internal standards enabled us to detect metabolites associated with postoperative delirium. Such methods should be considered for future metabolomics studies.

ANTICHOLINERGIC DRUGS: CUT-OFF FOR IMPAIRED COGNITION AND MOBILITY IN SENIORS

Elpidio K. ATTOH-MENSAH,[1] Gilles Loggia,[2] Remy Morello,[3] Pascale Schumann-Bard,[1] Pablo Descatoire,[2] Christian Marcelli,[3] and Chantal Chavoix[4], *1. Normandie Univ, UNICAEN, INSERM, COMETE, 14000 Caen, France, Caen, France, Metropolitan, 2. CHU Caen, Department of Geriatrics, Caen, France, Caen, France, Metropolitan, 3. CHU de Caen, Department of Statistics and Clinical Research, 14000 Caen, France, Caen, France, 4. Normandie Univ, UNICAEN, INSERM, COMETE, 14000 Caen, France, Caen, France*

Background and Objectives: Anticholinergic drugs are commonly prescribed in older adults despite growing evidence of their adverse outcomes. We aimed to improve knowledge about deleterious effects of anticholinergic drugs on both cognition and mobility, in particular whether there is a threshold value for the number of anticholinergic drugs or for the anticholinergic burden leading to mobility or cognitive impairment. Methods: 177 community-dwelling individuals aged 55 years or over, with a fall history in the previous year, took part in the study. Anticholinergic drugs were identified using the Anticholinergic Drug Scale (ADS), and global cognition and mobility were assessed using the Mini Mental State Examination (MMSE) and the Time-Up-and-Go (TUG) test, respectively. Results: ROC (Receiver Operating Characteristics) curve analysis indicated that consumption of a single anticholinergic drug per day was a risk

factor for impaired MMSE ($p < .05$) and TUG scores ($p < .05$). There was also a cut-off of anticholinergic burden of one for impaired MMSE scores ($p < .05$). Logistic regressions showed that impaired cognition induced by anticholinergic drugs were independent of confounding factors including comorbidities, while impaired mobility would be influenced by age and cardiac comorbidities. Conclusion: Daily consumption of a single anticholinergic drug, regardless of its anticholinergic burden, impairs both cognition and mobility community-dwelling seniors. Alternative solutions to anticholinergic drug prescription should thus be considered whenever possible.

HYPERTENSION DOES NOT CONTRIBUTE TO MICROBLEEDS ONSET IN FEMALE EFAD MICE

Mafalda Cacciottolo,[1] Todd E. Morgan,[2] and Caleb E. Finch[2], *1. University of Southern California, Los Angeles, California, United States, 2. Leonard Davis School of Gerontology, University of Southern California, Los Angeles, California, United States*

Cerebral microbleeds (MBs) contribute to pre-clinical cognitive decline and are an additional clinical burden in Alzheimer Disease (AD). Hypertension is associated with MBs, with nearly 2-fold higher likelihood for MBs per SD increment in blood pressure (BP). We investigated the possible role of age-related hypertension in the EFAD mouse model (transgenic for carrying familial AD mutations and targeted replacement of human APO-E3 or -E4). MBs were detected by Prussian Blue histochemistry. We extended prior findings with observations that MBs arise early in life, by 2 months, and confirmed female excess for ApoE3 and-E4 carriers. Wildtype C57BL/6J mice also accumulated MBs, and a 10-fold lower level and more slowly up to 21mo of age. BP was measured by the tail-cuff method. All mice had BP in the normotensive range, <150 mm Hg, systolic. Longitudinal measurements of blood pressure at ages 2, 4, and 6 months showed few age changes, except for E3FAD females at 6 months (systolic, +20%, $p<0.05$; diastolic, +33%, $p<0.05$). A possible decrease in blood pressure was observed in EFAD mice (-33%, $p<0.01$) compared to C57BL/6J mice. A not statistical trend of increase was observed in older C57BL/6J mice up to 18 mo of age, consistent with previous reports. Older ages are required for complete negation of role of hypertension in the MB model. Ongoing studies will examine mice older than 6 months for potential relations of blood pressure and MB, and in relation to brain amyloid deposits which surrounded MBs in our prior study.

NOVEL GAMMA-SECRETASE MODULATOR REGULATES APP PROCESSING AND INFLAMMATORY RESPONSES IN NPM-EXPOSED MICE

Carla D'Agostino,[1] Mafalda Cacciottolo,[1] Constantinos Sioutas,[2] Steven L Wagner,[3] Rudolph E Tanzi,[4] Todd E. Morgan,[5] and Caleb E. Finch[5], *1. University of Southern California, Los Angeles, California, United States, 2. Viterbi School of Engineering, University of Southern California, Los Angeles, California, United States, 3. Department of Neurosciences, University of California, San Diego, La Jolla, California, San Diego, United States, 4. Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, United States, 5. Leonard Davis School of Gerontology, University of Southern California, Los Angeles, California, United States*

Air pollution is associated with accelerated cognitive decline and increased risk of dementia in older populations (Cacciottolo et al 2017; Chen et al 2017). Rodent models of air pollution exposure also show Alzheimer-like changes including glial inflammatory responses and increased levels of endogenous amyloid beta (Aβ) peptides (Cacciottolo et al 2017 Levesque et al 2011). We hypothesized that pharmacological inhibition of Aβ production during nPM exposure would attenuate the amyloidogenic processing of APP and glial inflammatory responses. This hypothesis was tested using the γ-secretase modulator (GSM) (BPN-15606) which decreases Aβ42 levels in wild-type rodents (Wagner et al 2017; Kounnas et al. 2010). After nPM exposure of C57BL/6J male mice for 8 weeks, GSM-feeding attenuated pro-amyloidogenic and microglial inflammatory responses. Cerebral cortex levels of Aβ40 and 42 peptides were decreased by 35% and 45% respectively in mice exposed to filtered air and fed with GSM. Hippocampal levels of microglial Iba1 remained at control levels, a decrement of 50% below GSM treated mice. We suggest the Alzheimer candidate drug BPN-15606 has potential benefits to reducing the possible impact of urban air pollution in cognitive aging and Alzheimer risk. The attenuation of pro-amyloidogenic and microglial inflammatory responses is consistent with a role of endogenous Aβ levels in glial inflammatory responses and cognitive impairments from air pollution. Cacciottolo et al 2017, PMID 28140404; Chen H et al. 2017, PMID: 28917207; Levesque et al 2011, PMID 21864400; Wagner et al 2017, PMID 28416568; Kounnas 2010, PMID 20826309 Funding: P01 AG055367, R21AG050201, Cure Alzheimer's Fund

BIOLOGICAL MARKERS OF AGING: CHRONIC STRESS AND COGNITIVE IMPAIRMENT IN RESPONDERS FROM THE WORLD TRADE CENTER

Erica D. Diminich,[1] Sean Clouston,[1] Stacey B. Scott,[2] Nikhil Palekar,[1] Erica D. santiago,[1] Evelyn Bromet,[1] and Benjamin Luft[1], *1. Stony Brook University, New York, United States, 2. Stony Brook University, Stony Brook, New York, United States*

Post-traumatic Stress Disorder (PTSD) is a stress related syndrome. Chronic PTSD has increasingly been associated with poor health outcomes, neurodegeneration and risk for cognitive impairment (CI). However, the biological mechanisms underlying the development and maintenance of symptoms and potential associations in accelerating aging are not well understood. The aim of this study was to evaluate whether specific biomarkers influence functional limitations and cognitive impairment in rescue and recovery workers (i.e. responders) from the attacks on the World Trade Center (WTC) in New York. Plasma biomarkers were collected during annual health and wellness visits at the WTC responder clinic between 2012 and 2014. Short Physical Performance Battery (SPPB) and clinical data were examined with prospective PTSD symptom scores collected during participant's initial enrollment into the parent study as early as 2002. We examined the relationship between